PATENT
ATTORNEY DOCKET NO. 06727/008002

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Stace Lindsay et al.	Confirmation No.:	8638
Serial No.:	10/030,351	Art Unit:	1632
Filed:	June 7, 2002	Examiner:	Valarie E. Bertoglio
Customer No.:	21559		
Title:	EXPRESSION OF SECRETED HUMAN ALPHA-FETOPROTEIN IN TRANSGENIC ANIMALS		

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SUPPLEMENTAL APPEAL BRIEF

In reply to the Notification of Non-Compliant Appeal Brief dated February 13, 2009, Appellants provide this Supplemental Appeal Brief, which complies with the requirements of 37 C.F.R. § 41.37 and includes copies of evidence previously entered in the record in this application and relied upon by Appellants in the present appeal.

The fee required by § 41.20 (b)(2) for this Appeal Brief was paid on December 9, 2008. Appended hereto are a Claims Appendix, a Related Proceedings Appendix, and an Evidence Appendix.

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Real Party in Interest

The real party in interest is Merrimack Pharmaceuticals, Inc., which is the sole assignee of the above-captioned application.

Related Appeals and Interferences

None.

Status of Claims

Claims 2-5 and 8-20 are cancelled.

Claims 1, 6, 7, and 21-27 are currently pending, stand twice rejected in a non-final Office Action dated January 30, 2008, and are under appeal.

Status of Amendments

No amendments have been entered subsequent to the non-final Office Action dated January 30, 2008.

Summary of Claimed Subject Matter

There are three pending independent claims and seven pending dependent claims.

Independent claim 1, and claim 25 dependent therefrom, are directed to a substantially pure nucleic acid molecule that includes a nucleic acid sequence encoding recombinant human alpha-fetoprotein (rHuAFP), a milk-specific promoter operably linked to the rHuAFP-encoding sequence, and a leader sequence that enables secretion of rHuAFP by milk-producing cells into

the milk of a mammal. The invention of claims 1 and 25 is described in original claim 1 and in the specification at, e.g., page 1, line 28, through page 2, line 4, and page 12, lines 25-26.

Independent claim 6, and claims 7 and 26 dependent therefrom, are directed to non-human mammal's milk that includes biologically active rHuAFP. The invention of claims 6, 7, and 26 is described in original claims 6 and 7 and in the specification at, e.g., page 3, lines 1-9, page 5, lines 8-11, page 6, lines 7-8, page 8, lines 14-18, page 9, lines 12-17, and page 12, lines 25-26.

Independent claim 21, and claims 22-24 and 27 dependent therefrom, are directed a non-human transgenic mammal that expresses biologically active rHuAFP in its milk; the genome of the mammal includes a transgene, which includes a nucleic acid sequence encoding rHuAFP, a milk-specific promoter operably linked to the rHuAFP-encoding sequence, and a leader sequence, that effects expression of rHuAFP in mammary epithelial cells of the mammal. The invention of claims 21-24 and 27 is described in original claims 3, 5, 10, and 11 and in the specification at, e.g., page 6, lines 7-8, and page 8, lines 14-18, page 12, lines 25-26, and page 15, line 4, through page 16, line 1.

The present inventors found that, despite scientific issues which rendered success impossible to predict, they were able to express a gene encoding rHuAFP (a protein with multiple therapeutic uses, including treatment of auto-immune diseases) in the mammary epithelial cells of transgenic mammals and recover this protein in a biologically active form from milk into which rHuAFP was secreted.

Ground of Rejection to be Reviewed on Appeal

There is one issue on appeal: whether the Office erred in rejecting claims 1, 6, 7, and 21-27 under 35 U.S.C. 103(a) for obviousness over Deboer (U.S. Patent No. 5,633,076; hereinafter "Deboer"), Clark (U.S. Patent No. 5,322,775; hereinafter "Clark"), or Lubon (U.S. Patent No. 5,831,141; hereinafter "Lubon") in view of Morinaga et al. (PNAS 80:4604-4608; 1983; hereinafter "Morinaga") and Bennett (Breast Cancer Res. Treatment 45:169-179, 1997; hereinafter "Bennett").[1]

Argument

The Legal Standard For Obviousness Under 35 U.S.C. § 103(a)

A claimed invention is unpatentable if the differences between it and the prior art are such that the claimed subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See* 35 U.S.C. § 103(a) (2003). Correspondingly, the conclusion regarding obviousness of a claimed invention is based upon the following four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness (*e.g.*, commercial success, long-felt but unsolved needs, failure of others). *See McNeil-PPC, Inc.*

[1] Appellants were informed by Examiner Bertoglio via voicemail on June 2, 2008, that the 35 U.S.C. § 112, first paragraph rejections made in the Non-Final Office Action dated January 30, 2008, (i.e., the rejection of claims 6, 7, 21-24, and 27 for new matter, the rejection of claims 6, 7, 21-24, and 27 for lack of enablement, and the rejection of claims 25-27 for lack of written description) were withdrawn by the Panel of Examiners in response to Appellants' Pre-Appeal Brief Request for Review and that only the rejection of claims 1, 6, 7, and 21-27 for obviousness was maintained. Accordingly, Appellants' brief is only directed to the outstanding obviousness rejection.

v. L. Perrigo Co., 67 U.S.P.Q.2D (BNA) 1649, 337 F.3d 1362, 1368 (Fed. Cir. 2003) (Citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)); MPEP § 2141.

"A prima facie case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)"; M.P.E.P. § 2144.05(III); emphasis added. *See also KSR International Co. v. Teleflex Inc.*, 82 U.S.P.Q.2d (BNA) 1385, 127 S. Ct. 1727, 1739-40 (2007)(explaining that when the prior art teaches away from a combination, that combination is more likely to be nonobvious). A reference teaches away when a skilled artisan, upon reading the reference, would be led on a divergent path from the one taken by the Appellants. Although "any need or problem known in the field of endeavor at the time of invention and addressed by the [present application] can provide a reason for combining the elements in the manner claimed" (*see KSR*, 127 S. Ct. at 1742), it is necessary for the Office to establish a sufficient basis for concluding that one skilled in the art would combine the reference teachings to yield the claimed invention. *See In re Icon Health and Fitness, Inc.*, 83 U.S.P.Q.2d (BNA) 1746, 496 F.3d 1374, 1381 (Fed. Cir. 2007).

The Rejection of Present Claims 1, 6, 7, and 21-27 for Obviousness Should be Reversed

DeBoer, Clark, Lubon, Morinaga, and Bennett, even if combined, do not teach or suggest the inventions of present claims 1, 6, 7, and 21-27. The Office admits that none of DeBoer, Clark, or Lubon teaches each and every limitation of the instant claims. In particular, the Office states that "[t]he only elements lacking from...[DeBoer, Clark, and Lubon], alone or in combination, is the sequence encoding AFP and motivation to use the sequence in the techniques

of any of DeBoer, Clark or Lubon" (see pp. 6-7 of Office Action dated October 31, 2005; emphasis added). Therefore, to remedy the deficiencies of DeBoer, Clark, and Lubon, the Office cites Morinaga and Bennett, stating that "Morinaga provided the additional teachings and motivation to apply the methods of each of DeBoer, Clark and Lubon to produce rHuAFP in the milk of mammals," while "Bennett supports a motivation to make recombinant AFP...[and] merely exemplifies the interest in producing large quantities of AFP" (Office Action dated January 30, 2007, pp. 3 and 4, respectively). This is classic impermissible hindsight. The Office's conclusion of obviousness can be distilled down to the following statement in the most recent Office Action:

> Deboer, Clark, and Lubon render making any protein of interest obvious in the absence of evidence to the contrary as each of these references teach the claimed technology with virtually any protein of interest. (Office Action, January 30, 2008, p. 7.)

The Office has articulated a new rule, not found in the M.P.E.P. or any other authority: no one can be granted a patent on the expression of any protein in the milk of a transgenic mammal, regardless of what the art teaches about that protein, and regardless of the results obtained by the inventors. This Office-made rule unfairly and improperly places the burden on Appellants to overcome what is in effect a ready-made *prima facie* case of obviousness, without the Office actually having to make the case. Here, even analyzing obviousness within the Office's erroneous framework, one of ordinary skill in the art would not combine DeBoer, Clark, or Lubon with Morinaga and Bennett to yield the invention of present claims 1, 6, 7, and 21-27. The rejection of claims 1, 6, 7, and 21-24 for obviousness over the combination of these publications should be reversed.

The Scope and Content of the Prior Art

Deboer discloses a method of producing transgenic non-human animals (i.e., non-human primates, mice, cattle, dogs, pigs, and sheep) that produce recombinant polypeptides (i.e., exogenous proteins: human milk proteins, such as lactoferrin, lysozyme, secreted immunoglobulins, lactalbumin, bile salt-stimulated lipase, human serum proteins, such as albumin, immunoglobulins, Factor VIII, Factor IX, protein C, and industrial enzymes, such as proteases, lipases, chitinases, and liginases, and endogenous proteins: bovine milk proteins, such as αS1, αS2, β- and κ-casein, β-lactoglobulin lactoferrin, lysozyme, cholesterol hydrolase, serum proteins, such as serum albumin, and proteinaceous hormones, such as growth hormones) in the milk of the female transgenic animals (see, e.g., col. 6, line 40, through col. 7, line 35). Deboer exemplifies the production of recombinant polypeptides in transgenic cows and mice. Deboer, despite listing many proteins to be expressed in the described system, fails to make mention of human alpha-fetoprotein (HuAFP).

Clark discloses a method of producing a recombinant polypeptide (i.e., peptide hormones, blood coagulation factors (e.g., factors VIII and IX or subunits thereof, blood proteins, e.g., beta-globin, and serum proteins, e.g., $alpha_1$-antitrypsin) proteins for foodstuffs, including natural or altered milk proteins of the host mammal, or enzymes) in the milk of a transgenic non-human mammal (i.e., mice, sheep, goats, pigs, and cattle; see, e.g., col. 1, line 39, through col. 2, line 11, col. 3, lines 58-66, and col. 18, line 25, through col. 19, line 11). Clark exemplifies the production of recombinant $alpha_1$-antitrypsin and Factor XI in transgenic sheep and recombinant beta lactoglobulin in mice. Clark also fails to mention HuAFP.

Lubon discloses the production of recombinant human protein C in the milk of a transgenic animal (i.e., a mouse, a rat, a rabbit, a pig, a sheep, a goat, or a cow; see, e.g., col. 3, line 39, through col. 5, line 55, and col. 7, lines 34-38). Lubon exemplifies the production of recombinant human protein C in transgenic mice and pigs. Lubon also fails to mention HuAFP.

As is acknowledged by the Office, none of Deboer, Clark, or Lubon, either alone or in combination, teaches or suggests a rHuAFP-encoding nucleic acid construct, a transgenic non-human mammal that expresses and secretes rHuAFP into its milk, methods of producing rHuAFP by using a transgenic non-human mammal to express and secrete rHuAFP into its milk, or milk of a transgenic non-human mammal that contains rHuAFP.

To remedy the deficiencies of Deboer, Clark, and Lubon, the Office cites Morinaga and Bennett, which the Office asserts identifies HuAFP as a protein of interest (see Office Action dated October 31, 2005, p. 7). Appellants have previously pointed out that Morinaga merely discloses the nucleic acid and predicted amino acid sequence of HuAFP, but does not teach or suggest the expression of rHuAFP in a transgenic non-human mammal under the control of a milk-specific promoter or the secretion of rHuAFP in the milk of that mammal based on the presence of a leader sequence, as is taught in the present specification and recited in present claims 1, 6, 7, and 21-27. Furthermore, Morinaga fails to provide any motivation to express human AFP using recombinant means of any sort.

Bennett discloses the expression of rHuAFP using an *E. coli* expression system (see, e.g., the Abstract). Bennett concludes that the "[a]vailability of large quantities of homogeneous, biologically active recombinant human AFP [using this *E. coli* expression system] will facilitate further studies of structure/function, mechanism, and therapeutic potential of this agent as a

regulator of breast cancer growth" (Abstract). Bennett, like Morinaga, fails to teach or suggest a nucleic acid molecule containing a nucleic acid sequence encoding rHuAFP, a milk-specific promoter, and a leader sequence. Bennett also fails to teach or suggest the expression and secretion of biologically active rHuAFP in the milk of a transgenic non-human mammal; Bennett is limited solely to the expression of rHuAFP in *E. coli*. Thus, nowhere does Morinaga or Bennett provide any teaching or suggestion to express rHuAFP in a transgenic non-human mammal, much less the production of a transgenic mammal capable of secreting rHuAFP into its milk.

The Differences Between the Claims and the Prior Art

The Prior Art Teaches Away from the Expression of rHuAFP in the Milk of a Transgenic Mammal

Even if Morinaga and Bennett could be read to direct the skilled artisan to express rHuAFP in the milk of a transgenic mammal according to the methods of Deboer, Clark, or Lubon, which they do not, publications available prior to Appellant's filing date direct the skilled artisan **away** from the expression of rHuAFP in milk. As was discussed in the Reply to Office Action filed on October 31, 2007, milk is known to contain an abundant amount of free fatty acids (FFAs), including mono- and poly-unsaturated acids (see Table 3 from "Compositions of Foods; Dairy and Egg Products"; Agricultural Handbook No. 8-1, Agricultural Research Service; a copy of which was filed as Exhibit A with the Reply to Office Action on October 31, 2007).

This fact is highly relevant to the issue of predictability, and thus, obviousness. Unsaturated fatty acids were known to inhibit the biological activity of both mouse, rat, and

human AFPs, as determined by detecting conformational changes in AFP that affect its estrogen binding and immunoreactivity (see pp. 8-10 of the Reply to Office Action dated October 31, 2007; Vallette et al., Biochim. Biophys. Acta 997:302-312, 1989; Haourigui et al., Biochimica et Biophysica Acta 1125:157-165, 1992; and Parmelee et al., J. Biol. Chem. 253:2114-2119, 1978). Inhibition of AFP biological activity is dose-dependent and varies with the degree of fatty acid unsaturation.

And, in fact, the inventors demonstrated experimentally that HuAFP secreted into the milk of a transgenic goat does indeed bind FFAs present therein (see Reply to Office Action dated October 31, 2007, p. 9). Thus, contrary to the Office's conclusion, given the time and expense required to produce a transgenic mammal, one skilled in the art, having knowledge of, e.g., Vallete et al., Haourigui et al., and Parmelee et al., all of which teach that HuAFP, when exposed to an environment rich in FFAs, will bind to FFAs that induce changes in the conformation and biological activity of HuAFP, would not seek to produce biologically active rHuAFP in the milk of a transgenic mammal.

Thus, the inventors succeeded in the face of the prior art, which taught **away** from the expression of rHuAFP in the milk of a transgenic mammal. Vallete et al., Haourigui et al., and Parmelee et al., among others, teach away from the use of Appellants' claimed compositions and methods (see *In re Geisler*, *supra*, and *KSR*, *supra*); the skilled artisan had no motivation to combine Deboer, Clark, or Lubon with Morinaga and Bennett to yield the invention of present claims 1, 6, 7, and 21-27, and as is discussed below, would have had no basis to expect success.

There would have been no Reasonable Expectation that Expressing rHuAFP in the Milk of a Transgenic Mammal would be Successful

Even if the Board disagrees that the prior art teaches away from the invention of present claims 1, 6, 7, and 21-24, the claims are patentable because there would have been no expectation that the invention would succeed. The *KSR* court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp" (*KSR*, 127 S. Ct. at 1732; emphasis added). Under these circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here.

As is discussed above, none of Deboer, Clark, Lubon, Morinaga, and Bennett, either singly or in combination, teaches or suggests the expression of rHuAFP in the milk of a transgenic mammal. Just as importantly, Deboer, Clark, Lubon, Morinaga, and Bennett contain nothing that would have given rise to a reasonable expectation that rHuAFP could be successfully expressed in the milk of a transgenic mammal in a biologically active form.

As is discussed above, Morinaga and Bennett are silent on the expression of any protein, much less rHuAFP, in a transgenic mammal, and none of Deboer, Clark, or Lubon provides any suggestion to express rHuAFP in the milk of a transgenic mammal, much less evidence that rHuAFP can be expressed in the milk of a transgenic mammal in a biologically active form. Moreover, as is discussed above, the prior art teaches that FFAs induce conformational changes in HuAFP that affect at least some of its biological activities. The skilled artisan, recognizing the prior art teaching that milk contains a significant number of FFAs, would have no reasonable

basis to conclude that the expression of rHuAFP in the milk of a transgenic mammal would yield a biologically active protein.

The Office disagreed with this point, stating:

> First, that some property or properties of rHuAFP *may* be altered by binding or other natural interaction with some fatty acids in milk, *does not indicate that all, if any, properties will be affected by the levels of specific fatty acids that are present in milk.* Binding of a fatty acid as a ligand would be considered a natural property of AFP and *it is not clear that this would be undesirable.* It is also noted that Vallette teaches that the identity and quantity of fatty acids present is important in the inhibition of estrogen binding and thus such variability in the effect of various fatty acids on AFP would likely hold true for other activities of AFP, *making it unpredictable which, if any, activities of AFP would be altered in milk.* Second, the study of Vallette consisted of an unnatural, in vitro situation of incubating AFP with free fatty acids. Neither Applicant nor Vallette provide a nexus between this study and what occurs in vivo in the mammary gland. *The in vivo physiology is vastly different from an in vitro environment and the interactions that the free fatty acids may have with other proteins, as well as with AFP, differ.* (Office Action, p. 5; emphasis added.)

Yet, as shown by the italicized statements above, even in challenging Appellants' position, the Office acknowledges the unpredictability of expressing biologically active rHuAFP in the milk of a transgenic mammal.

As stated by the *KSR* court, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (*Id.* at 1739, 82 USPQ2d at 1395). Here, the fact that "some property or properties of rHuAFP *may* be altered by binding or other natural interaction with some fatty acids in milk" places doubt on the likelihood that the production of a biologically active rHuAFP in a transgenic mammal will be successful. One of skill in the art would not know, *a priori*, whether expression of rHuAFP in the milk of a transgenic mammal would yield a rHuAFP having the desired biological activity.

The field of the invention is the production of active, therapeutically useful recombinant proteins in animals. There can be no disagreement as to whether this field is unpredictable; indeed, the MPEP, § 2164.03, refers to "cases involving unpredictable factors, such as most chemical reactions and physiological activity...." Of course, reasonable likelihood of success varies inversely with unpredictability.

In fact, Lubon confirms that the expression of recombinant proteins, in particular protein C, in a transgenic mammal is highly unpredictable and may result in the expression of a significant amount of biologically *inactive* protein (i.e., ~60-70% of the expressed protein C is inactive; see col. 3, lines 3-36, of Lubon). Lubon purports to solve the problems associated with the expression of protein C in the milk of a transgenic mammal, but fails to address the other, different factors that would be faced by a scientist attempting to produce a different recombinant protein expressed in the milk of a transgenic mammal.

The Office states that the difficulties addressed by Lubon, which involve "the lack of post-translational modifications of protein in mammary epithelial cells" (Office Action dated January 30, 2008, p. 8), are irrelevant to the production of biologically active rHuAFP in mammary epithelial cells because rHuAFP "has been made in both E.coli and yeast and has been found to be active despite a lack of post-translational processing (*Id.* at p. 8). The Office again misses the point. As recognized by the prior art, the recombinant expression of proteins in the foreign environment of the mammary gland is rife with potential problems and uncertainties, only one of which is the effect of post-translational modifications on the expressed protein.

As is discussed above, prior to Applicants' filing date the skilled artisan was well aware that the binding of FFAs to AFP induces a conformational change in AFP that inhibits its

biological activity (see Vallete et al., Haourigui et al., and Parmelee et al., discussed above). Because FFAs are present in significant amounts in the milk of mammals, one skilled in the art, having knowledge of Vallete et al., Haourigui et al., and Parmelee et al., and absent evidence to the contrary, would have no reasonable expectation that the expression of rHuAFP in the milk of a transgenic mammal would yield biologically active rHuAFP; nothing in Deboer, Clark, Lubon, Morinaga, or Bennett changes this conclusion. Thus, one of skill in the art could not have known, *a priori*, how FFAs in milk would have affected the biological activity of rHuAFP upon its expression into milk. Until Appellants described the successful expression and recovery of biologically active rHuAFP from the milk of a transgenic mammal, the art did not recognize that such action could be performed successfully.

The Office dismisses this point by stating:

> Thus, there is no indication what changes, if any, in the properties of AFP will occur when the AFP is produced in the mammary environment. In fact, as supported by the post-filing art, rHuAFP appears identical when isolated from milk of a transgenic mammal as compared to AFP isolated from human cord blood (see Parker, 2004, of record, page 151, paragraph bridging columns)...Parker also noted similar pharmacokinetics and functionality of the rHuAFP isolated from milk of a transgenic mammal and AFP isolated from cord blood (paragraph bridging columns at page 182-col. 2, paragraph 2). (Office Action dated January 30, 2008, p. 6.)

The Office's position is simply impermissible hindsight reconstruction. It is improper for the Office to use the post-filing publication, Parker *et al.* (2004), which is Appellant's own publication, to support its position that the expression of rHuAFP into milk would have been obvious; prior to Appellants' filing date, this information was not known in the art.

Thus, contrary to the Office's position, none of Deboer, Lubon, or Clark provides any reasonable basis to conclude that any serum protein, and certainly not rHuAFP, can be

successfully expressed in the milk of a transgenic mammal in a biologically active form. For this reason, Deboer, Clark, and Lubon fail to provide the skilled artisan with any reasonable expectation of success with respect to the expression of biologically active rHuAFP in the milk of a transgenic mammal.

Finally, the Office fails to consider that the expression of rHuAFP in the milk of a transgenic mammal is itself unnatural. Because Vallette and the other cited publications clearly provide evidence of the inhibitory effect of FFAs on the biological activity of rHuAFP, when properly considered, these publications, at the least, render a method of producing biologically active rHuAFP in fatty acid rich environments, such as milk, unpredictable. In the alternative, and as discussed above, the publications cited by Appellants teach away from the invention of present claims 1, 6, 7 and 21-27.

The Office attempts to dispel the shadow of unpredictability cast by Vallette by stating that "AFP has been isolated from a number of sources including E. coli, yeast, cord blood and fetal liver and is active in each of these cases" (Office Action, p. 7). The Office concludes by stating that "specific teachings suggesting rHuAFP isolated from milk would not be active <u>are necessary to support an argument</u> that there was not a reasonable expectation of success at filing" (Office Action dated January 30, 2008, p. 7; emphasis added). This position is untenable.

As is discussed above, the Office acknowledges that one cannot predict which, if any, activities of AFP would be altered in milk. Furthermore, the ability to express biologically active rHuAFP in *E. coli*, yeast, cord blood, and fetal liver, none of which contain the large amount of fatty acids that are present in milk, provides no reasonable expectation that the expression of biologically active rHuAFP in milk would be successful. Applicants' evidence

raises substantial doubt regarding the predictability of expressing biologically active rHuAFP in fatty acid rich environments, such as the milk of a transgenic mammal. The Office has not properly considered Appellants' evidence and has simply taken the position that present claims 1, 6, 7, and 21-27 are *per se* obvious because expression of any protein in any transgenic mammal is obvious in view of Deboer, Clark, and Lubon.

The M.P.E.P. § 2144.08 (II) makes clear that this position is improper, stating that the "[u]se of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103." Furthermore, when determining whether a claimed species, here the production of biologically active rHuAFP in the milk of a transgenic mammal, would have been obvious to one of ordinary skill in the pertinent art at the time the invention was made, the Office must consider the facts of the particular case in view of the totality of the circumstances (M.P.E.P. § 2144.08 (II)); this the Office has failed to do.

In this case, the Office has combined DeBoer, Clark, or Lubon with Morinaga and Bennett without evidence of any suggestion, teaching, or motivation to do so and has disregarded evidence that suggests the unpredictability of, or the teaching away from, the invention of present claims 1, 6, 7, and 21-27. For all of these reasons, Appellants respectfully submit that the rejection of claims 1, 6, 7, and 21-27 under 35 U.S.C. § 103(a) for obviousness over DeBoer, Clark, or Lubon in view of Morinaga and Bennett should be reversed.

CONCLUSION

For all the reasons provided above, the real party in interest, Merrimack Pharmaceuticals, Inc., a small entity, respectfully requests that the Board reverse the Office's rejection of pending claims 1, 6, 7, and 21-27.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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Date: 5 March 2009

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Claims Appendix:

Claims on Appeal

1. (Rejected) A substantially pure nucleic acid molecule comprising: (i) a nucleic acid sequence encoding recombinant human alpha-fetoprotein (rHuAFP), (ii) a milk-specific promoter, said promoter being operably linked to said rHuAFP-encoding sequence, and (iii) a leader sequence encoding a protein secretory signal that enables secretion of said rHuAFP by milk-producing cells into the milk of a mammal.

2-5 (Cancelled)

6. (Rejected) Non-human mammal's milk comprising biologically active recombinant human alpha-fetoprotein (rHuAFP).

7. (Rejected) The milk of claim 6, wherein the rHuAFP is soluble and is produced by a non-human transgenic mammal whose genome comprises a transgene that effects expression of said rHuAFP in mammary epithelial cells of said mammal, wherein said transgene comprises: (i) a nucleic acid sequence encoding rHuAFP, (ii) a milk-specific promoter, said promoter being operably linked to said rHuAFP-encoding sequence, and (iii) a leader sequence encoding a protein secretory signal that enables secretion of said rHuAFP by said mammary epithelial cells into the milk of said mammal.

8-20 (Cancelled)

21. (Rejected) A non-human transgenic mammal that expresses biologically active recombinant human alpha-fetoprotein (rHuAFP) in its milk, wherein the genome of said mammal comprises a transgene that effects expression of rHuAFP in mammary epithelial cells of said mammal, wherein said transgene comprises: (i) a nucleic acid sequence encoding rHuAFP, (ii) a milk-specific promoter, said promoter being operably linked to said rHuAFP-encoding

sequence, and (iii) a leader sequence encoding a protein secretory signal that enables secretion of said rHuAFP by said mammary epithelial cells into the milk of said mammal.

22. (Rejected) The non-human transgenic mammal of claim 21, wherein the mammal is a goat, a cow, a sheep, or a pig.

23. (Rejected) A method for preparing biologically active recombinant human alpha-fetoprotein (rHuAFP) comprising the steps of:

(a) providing the non-human transgenic mammal of claim 21; and

(b) collecting milk containing said rHuAFP from said mammal.

24. (Rejected) The method of claim 23, further comprising step (c) purifying said rHuAFP from said milk.

25. (Rejected) The nucleic acid molecule of claim 1, wherein said nucleic acid sequence is modified to express said rHuAFP in a non-glycosylated form.

26. (Rejected) The milk of claim 7, wherein said transgene is modified to express said rHuAFP in a non-glycosylated form.

27. (Rejected) The non-human transgenic mammal of claim 21, wherein said transgene is modified to express said rHuAFP in a non-glycosylated form.

Related Proceedings Appendix

There are no pending interferences related to this case.

Evidence Appendix

Appellants provide the following evidence in support of this Brief on Appeal:

1) "Compositions of Foods; Dairy and Egg Products," Agricultural Handbook No. 8-1, Agricultural Research Service, Washington, D.C.; USDA, 1976. This evidence was made of record as Exhibit A in the Reply to Office Action filed on October 31, 2007.

2) Vallette et al., "Confomrational Changes in Rodent and Human α-Fetoprotein: Influence of Fatty Acids," Biochim. Biophys. Acta 997:302-312, 1989. This evidence was made of record as Exhibit B in the Reply to Office Action filed on October 31, 2007.

3) Haourigui et al., "*In vivo* Transient Rise in Plasma Free Fatty Acids Alters the Functional Properties of α-Fetoprotein," Biochimica et Biophysica Acta 1125:157-165, 1992. This evidence was made of record as Exhibit C in the Reply to Office Action filed on October 31, 2007.

4) Parmelee et al., "The Presence of Fatty Acids in Human α-Fetoprotein," J. Biol. Chem. 253:2114-2119, 1978. This evidence was made of record as Exhibit D in the Reply to Office Action filed on October 31, 2007.